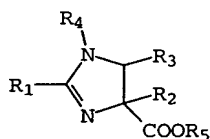


I CLAIM:

-1-

An imidazoline ester of the formula:



5

10

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members with O, N, S or combinations thereof, and heterocyclic containing 5 to 12 ring members with O, N, S; and R<sub>5</sub> a group which provides the ester of the imidazoline.

-2-

The imidazoline of Claim 1 wherein R<sub>1</sub> is phenyl.

-3-

The imidazoline of Claim 1 wherein R<sub>4</sub> is benzyl.

-4-

The imidazoline of Claim 1 wherein R<sub>5</sub> is lower alkyl containing 1 to 4 carbon atoms.

-5-

The imidazoline of Claim 4 wherein R<sub>5</sub> is ethyl.

-6-

The imidazoline of Claim 1 wherein R<sub>2</sub> is lower alkyl containing 1 to 4 carbon atoms.

-7-

The imidazoline of Claim 6 wherein R<sub>2</sub> is methyl.

-8-

The imidazoline of Claim 1 wherein R<sub>3</sub> is selected from the group consisting of phenyl and substituted phenyl.

-9-

The imidazoline of Claim 1 wherein R<sub>1</sub> is phenyl, R<sub>2</sub> is methyl, R<sub>3</sub> is phenyl, and R<sub>4</sub> is benzyl.

-10-

The imidazoline of Claim 1 wherein R<sub>1</sub> is phenyl, R<sub>2</sub> is methyl, R<sub>3</sub> is 4-methoxyphenyl, and R<sub>4</sub> is benzyl.

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The imidazoline of Claim 1 wherein R<sub>1</sub> is phenyl, R<sub>2</sub> is methyl, R<sub>3</sub> is phenyl, and R<sub>4</sub> is 4-fluorophenyl.

-12-

The imidazoline of Claim 1 wherein R<sub>1</sub> is phenyl, R<sub>2</sub> is phenyl, R<sub>3</sub> is phenyl, and R<sub>4</sub> is benzyl.

-13-

The imidazoline of Claim 1 wherein R<sub>1</sub> is phenyl, R<sub>2</sub> is 1H-indol-3-ylmethyl, R<sub>3</sub> is phenyl, and R<sub>4</sub> is benzyl.

-14-

The imidazoline of Claim 1 wherein  $R_1$  is phenyl,  $R_2$  is methyl,  $R_3$  is pyridin-4-yl, and  $R_4$  is benzyl.

-15-

The imidazoline of Claim 1 wherein  $R_1$  is phenyl,  $R_2$  is methyl,  $R_3$  is phenyl, and  $R_4$  is H.

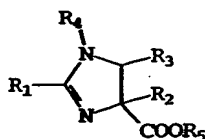
-16-

The imidazoline of Claim 1 wherein  $R_1$  is phenyl,  $R_2$  is methyl,  $R_3$  is ethoxycarbonyl, and  $R_4$  is H.

-17-

The imidazoline of Claim 1 wherein  $R_1$  is phenyl,  $R_2$  is methyl,  $R_3$  is pyridin-4-yl, and  $R_4$  is benzyl.

An imidazoline ester of the formula:



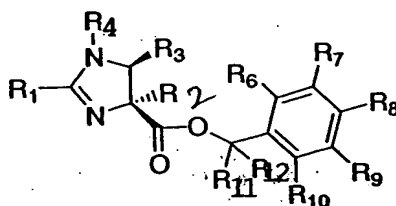
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members with O, N, S or combinations thereof, and heterocyclic containing 5 to 12 ring members with O, N or S or combinations thereof; and R<sub>5</sub> a group which provides the ester of the imidazoline; and R<sub>5</sub> is an ester group containing 1 to 15 carbon atoms which are alkyl, cycloalkyl, aryl, heteroaryl comprising O, N or S or combinations thereof and heterocyclic comprising O, N, S or combinations thereof and wherein the carbon atoms are optionally substituted with a halogen.

The imidazoline of Claim 18 wherein R<sub>1</sub> and R<sub>3</sub> are phenyl, R<sub>4</sub> is lower alkyl containing 1 to 4 carbon atoms and R<sub>5</sub> is benzyl.

The imidazoline of Claim 19 wherein R<sub>5</sub> is a benzyl group.

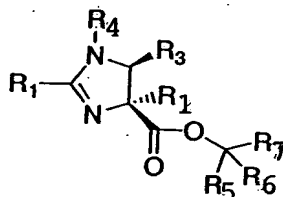
The imidazoline of claim 19 wherein R<sub>5</sub> is 1-phenyl-ethyl.

An imidazoline ester of the formula:



wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members with O, N, S or combinations thereof, and heterocyclic containing 5 to 12 ring members with O, N or S or combinations thereof; and wherein in the ester group  $R_{11}$  and  $R_{12}$  are selected from the group consisting of a hydrogen, alkyl, aryl, arylalkyl and a halogen, and  $R_6$  to  $R_{10}$  are selected from the group consisting of hydrogen, halogen, alkyl halide, ether, cyclic ether, cyclic alkyl, aryl or acyl, amine, hydroxyl and heterocyclic or heteroaryl rings with O, N or S or combinations thereof comprising 5 to 14 carbon atoms.

The present invention relates to an imidazoline of the formula:

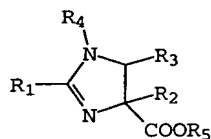


wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members with O, N, S or combinations thereof, and heterocyclic containing 5 to 12 ring members with O, N or S or combinations thereof; and R<sub>5</sub> is a group which provides the ester of the imidazoline, wherein R<sub>5</sub> and R<sub>6</sub> are selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl and halogen and wherein R<sub>7</sub> is selected from the group consisting of aryl and heterocyclic group containing one or more N, S, or O or combinations thereof comprising 5 to 14 carbon atoms.

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A method for inhibiting inflammation in a mammal which comprises administering an imidazoline ester of the formula:

5



10 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group  
consisting of aryl, arylalkyl, heteroaryl containing 5  
to 14 ring members, and heterocyclic containing 5 to 12  
ring members; and R<sub>5</sub> is a group which provides the ester,  
all of which are optionally substituted, to the mammal  
15 in an amount sufficient to inhibit the inflammation.

-25-

The method of Claim 24 wherein the mammal is human.

-26-

The method of Claim 24 wherein the mammal is a lower mammal.

-27-

The method of any one of Claims 24, 23 or 24 wherein the administration is orally to the mammal.

-28-

The method of any one of Claims 24, 25 or 26 wherein the administration is topically to the mammal.

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-29-

The method of any one of Claims 24, 25 or 26 wherein the administration is by injection into the mammal.

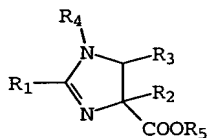
-30-

The method of any one of Claims 24, 25 or 26 wherein the administration is intravenous into the mammal.

-31-

A method for inhibiting a microorganism which comprises:

administering an effective amount of an imidazoline ester of the formula:



10 wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members, and heterocyclic containing 5 to 12 ring members; and  $R_5$  is a group which  
15 provides the ester, all of which are optionally substituted, to inhibit the microorganism.

-32-

The method of Claim 31 wherein the inhibition is *in vitro*.



-33-

The method of Claim 31 wherein the inflammation is *in vivo*.

-34-

The method of Claim 31 wherein the administration is to a mammal.

-35-

The method of Claim 34 wherein the mammal is human.

-36-

The method of any one of Claims 31, 32 or 33 wherein the administration is orally to a mammal.

-37-

The method of any one of Claims 31, 32 or 33 wherein the administration is by injection into a mammal.

-38-

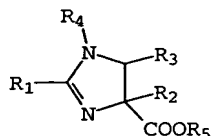
The method of any one of Claims 31, 32 or 33 wherein the administration is intravenously into a mammal.

-39-

The method of any one of Claims 31, 32 or 33 wherein the administration is topically to a mammal.

A method of inhibiting degradation of a protein which is NF- $\kappa$ B or NF- $\kappa$ B kinase which comprises contacting the protein with a imidazoline ester of the formula:

5



10 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members, and heterocyclic containing 5 to 12 ring members; and R<sub>5</sub> is a group which provides the ester, all of which are optionally  
15 substituted.

The method of Claim 40 wherein the inhibition is *in vivo*.

The method of Claim 40 wherein the inhibition is in the treatment of cancer.

A method for inhibiting inflammation in a mammal which comprises administering a multi-substituted 4-acid or 4-alkyl ester imidazoline to the mammal in an amount sufficient to inhibit the inflammation.

-44-

A method of inhibiting degradation of a protein which is NF- $\kappa$ B or NF- $\kappa$ B kinase which comprises contacting the protein with a multi-substituted imidazoline ester in an amount sufficient to inhibit degradation of the protein.

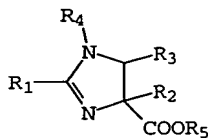
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-45-

A method of inhibiting a cancer which comprises contacting the cancer with a multi-substituted imidazoline ester in an amount sufficient to inhibit the cancer.

A method for inhibiting a tumor or cancer in a mammal which comprises administering an imidazoline ester of the formula:

5



10 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group  
consisting of aryl, arylalkyl, heteroaryl containing 5  
to 14 ring members, and heterocyclic containing 5 to 12  
ring members; and R<sub>5</sub> is a group which provides the ester,  
all of which are optionally substituted, to the mammal  
15 in an amount sufficient to inhibit the tumor or cancer.

The method of Claim 46 wherein the mammal is human.

The method of Claim 46 wherein the mammal is a lower mammal.

The method of any one of Claims 46, 47 or 48 wherein the administration is orally to the mammal.

The method of any one of Claims 46, 47 or 48 wherein the administration is topically to the mammal.

-51-

The method of any one of Claims 46, 47 or 48 wherein the administration is by injection into the mammal.

-52-

The method of any one of Claims 46, 47 or 48 wherein the administration is intravenous into the mammal.

-53-

The method of Claim 46 wherein the imidazoline is admixed with a drug which inhibits growth of the tumor or cancer.

-54-

The method of Claim 46 wherein the drug is a platinate.

-55-

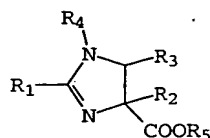
The method of Claim 46 wherein the drug is camptothecin.

-56-

The method of any one of Claims 46, 47 or 48.

-57-

A composition which comprises an imidazoline  
of the formula



10 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are selected from the group  
consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl  
containing 5 to 14 ring members, and heterocyclic  
containing 5 to 12 ring members; and R<sub>5</sub> is a group which  
provides the ester, all of which are optionally  
substituted; and

15 (b) a drug which inhibits growth of the tumor  
or cancer.

-58-

The composition of Claim 57 wherein the drug  
is a platinate.

-59-

The composition of Claim 57 wherein the drug  
is camptothecin.

-60-

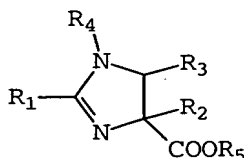
The composition of any one of Claims 57, 58 or  
59 with a pharmaceutical carrier.

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-61-

A method for inhibiting an immune response to a foreign NF- $\kappa$ B activator introduced into a mammal which comprises:

administering an effective amount of an imidazoline ester of the formula:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are each individually selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members, and heterocyclic containing 5 to 12 ring members; and, R<sub>5</sub> is a group which provides the ester, all of which are optionally substituted, to the mammal so as to thereby inhibit the immune response to the foreign NF- $\kappa$ B activator.

-62-

The method of Claim 61 wherein R<sub>1</sub> is phenyl.

-63-

The method of Claim 61 wherein R<sub>4</sub> is benzyl.

-64-

The method of Claim 61 wherein R<sub>5</sub> is lower alkyl containing 1 to 4 carbon atoms.

-65-

The method of Claim 61 wherein R<sub>5</sub> is ethyl.

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-66-

The method of Claim 61 wherein  $R_2$  is lower alkyl containing 1 to 4 carbon atoms.

-67-

The method of Claim 61 wherein  $R_2$  is methyl and  $R_3$  is selected from the group consisting of phenyl and substituted phenyl.

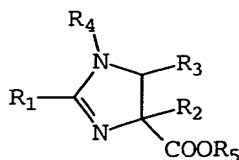
-117-



-68-

A method for treating an autoimmune disease in a mammal without bringing on complete immunodeficiency in the mammal which comprises:

administering an effective amount of an imidazoline ester of the formula:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are each individually selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members, and heterocyclic containing 5 to 12 ring members; and, R<sub>5</sub> is a group which provides the ester, all of which are optionally substituted, to the mammal so as to treat the autoimmune disease.

-69-

The method of Claim 68 wherein R<sub>1</sub> is phenyl.

-70-

The method of Claim 68 wherein R<sub>4</sub> is benzyl.

-71-

The method of Claim 68 wherein R<sub>5</sub> is lower alkyl containing 1 to 4 carbon atoms.

-72-

The method of Claim 68 wherein R<sub>5</sub> is ethyl.

-118-

-73-

The method of Claim 68 wherein  $R_2$  is lower alkyl containing 1 to 4 carbon atoms.

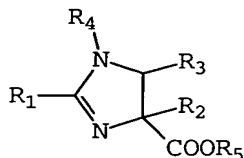
-74-

The method of Claim 68 wherein  $R_2$  is methyl and  $R_3$  is selected from the group consisting of phenyl and substituted phenyl.

-75-

A method for inhibiting rejection of an organ transplanted into a mammal which comprises:

administering an effective amount of an imidazoline ester of the formula:



wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are each individually selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members, and heterocyclic containing 5 to 12 ring members; and,  $R_5$  is a group which provides the ester, all of which are optionally substituted, to the mammal so as to inhibit rejection of the organ transplanted into the mammal.

-76-

The method of Claim 75 wherein  $R_1$  is phenyl.

-77-

The method of Claim 75 wherein  $R_4$  is benzyl.

-119-

-78-

The method of Claim 75 wherein  $R_5$  is lower alkyl containing 1 to 4 carbon atoms.

-79-

The method of Claim 75 wherein  $R_5$  is ethyl.

-80-

The method of Claim 75 wherein  $R_2$  is lower alkyl containing 1 to 4 carbon atoms.

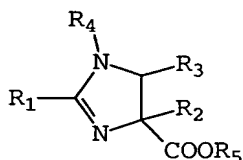
-81-

The method of Claim 75 wherein  $R_2$  is methyl and  $R_3$  is selected from the group consisting of phenyl and substituted phenyl.

-82-

A method for inhibiting reactivation of human immunodeficiency virus (HIV) in cells latently infected with the HIV which comprises:

administering an effective amount of an imidazoline ester of the formula:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are each individually selected from the group consisting of alkyl, acyl, aryl, arylalkyl, heteroaryl containing 5 to 14 ring members, and heterocyclic containing 5 to 12 ring members; and, R<sub>5</sub> is a group which provides the ester, all of which are optionally substituted, to inhibit the reactivation of the HIV in the latently infected cells.

-83-

The method of Claim 82 wherein R<sub>1</sub> is phenyl.

-84-

The method of Claim 82 wherein R<sub>4</sub> is benzyl.

-85-

The method of Claim 82 wherein R<sub>5</sub> is lower alkyl containing 1 to 4 carbon atoms.

-86-

The method of Claim 82 wherein R<sub>5</sub> is ethyl.

-121-

-87-

The method of Claim 82 wherein  $R_2$  is lower alkyl containing 1 to 4 carbon atoms.

-88-

The method of Claim 82 wherein  $R_2$  is methyl and  $R_3$  is selected from the group consisting of phenyl and substituted phenyl.

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The method of Claim 46 wherein the drug is a topoisomerase II inhibitor.

-90-

The method of Claim 89 wherein the drug is daunomycin.

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